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Chemical:	**Pyrethrins**
PC Code:	**069001**
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Memo Date:	**10/13/88**
File ID:	**00000000**
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HED Records Reference Center
12/26/2001

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CASWELL FILE

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OPP OFFICIAL RECORD
HEALTH EFFECTS DIVISION
SCIENTIFIC DATA REVIEWS
EPA SERIES 361

OCT 13 1988

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT; EPA Identifying Number 069001. Pyrethrins: Studies submitted to help resolve problems related to completion of the plant and animal metabolism data requirements.

TOX CHEM. No.: 715
TOX PROJECT No.: 8-0905
Record No.: 224254

FROM: John Doherty 10/7/88
Section I, Toxicology Branch I (IRS)
Health Effects Division (TS-769)

TO: Geraldine Werdig
Chief, DATA-CALL-IN Section
Product Manager Team #50
Registration Division (TS-767)

THROUGH: Edwin Budd
Section Head
Section I, Toxicology Branch I (IRS)
Health Effects Division (TS-769)

10/11/88

10/13/88

Background.

The Pyrethrin Steering Committee/Chemical Specialties Manufacturing Association (PSC/CSMA) has submitted two volumes containing 13 published papers or other submissions related to the photolysis, plant and animal metabolism of pyrethrins and/or pyrethroids. The purpose of submitting this information was to satisfy the Agency's need to further characterize the metabolism and photodegradation of pyrethrins in accordance with the conditions indicated in the letter (dated April 4, 1988) from Richard Tinsworth (Director, Registration Division) to Jim T. Hill (Director, Pyrethrin Task Force, Pyrethrin Steering Committee).

Toxicology Branch has reviewed the information as submitted (refer to lists of studies submitted, attached) and the following comments apply.

Toxicology Branch Comments.

1. Most of these studies (Documents 2, 3, 4, 5, 6, and 7 in Volume I, and 8 in Volume II) relate to the responsibilities of Residue Chemistry Branch). TB has no further comment on the acceptability of these studies to satisfy Residue Chemistry Branch requirements.

2. Documents 4, 6, and 7 in Volume II contain information on pyrethroids, which are synthetic analogs based on the chemical structure of the natural pyrethrins. This information is of limited value to meeting the data requirements related to the metabolism of the natural pyrethrins. Pyrethroids have a wide range of both alcoholic and acidic side chains which affect the metabolism and result in a variety of metabolites and thus do not provide useful surrogate data for pyrethrin metabolism. (Note: Information on allethrin is considered an exception since this chemical closely resembles the natural pyrethrins in structure). Data Evaluation Records were not prepared for these items.

3. Documents 1, 2, 3 and 4 of Volume II are related to papers by Dr. J.E. Casida and his colleagues. This information was previously reviewed by TB (refer to memo from J. Doherty dated April 18, 1988 for EPA File Symbol 52563-R, attached). This review indicated that the publications by Dr. Casida have been classified as SUPPLEMENTARY because the data are submitted in publication form and no original data are included. It was also indicated in the review of these studies that the registrant or Dr. Casida's group would have to define how the stereo-configuration of the radiolabelled and nonlabelled pyrethrins synthesized for these studies can be shown to be of the same stereoconfiguration as the natural pyrethrins. The registrant has not replied to this inquiry. [Note: TB's review of Casida's papers on the metabolism of pyrethrins in rats was prepared in response to information submitted by the U.S. Pyrethrin Culture, apparently a separate business concern from the Pyrethrin Steering Committee].

Deposition Letter

1

Shrader Analytical & Consulting Laboratorie:
Analysis of Photolysis products of Pyrethrur
Extract by GC/MS - Report.

2

Composite Oxidative (uv) Chart for
isomerization of Pyrethrins.

3

Chen, Yuh-Lin & Casida J.E. (1969) "Photodecomposition of Pyrethrin 1, Allethrin, Phthalthrin, and Dimethrin" Ag. & Food Chem. Vol. 17, No 2. page 208.
Ruzo, L.O.,(1982)"Photochemical Reactions of The Synthetic Pyrethroids".Progress in Biochemistry Vol 2. John Wiley.

4

Bullivant M.J. & Pattenden, G.(1971)"Photo--chemical decomosition of Chrysanthemic Acid & its Alkyl Esters. Pyrethrum Post, Vol 11, No. 2. pp72-76.

5

Bullivan M.J. & Pattenden, G.(1973)"Fundament photodegradation Pathways for Rethrolone moieties of the Pyrethrins Insecticides. Vol No 2. pp64-75.

6

Abe, Y., Tsuda, K. & Fujita, Y. (1972)"Stud on Pyrethroidal Compounds PartIII. Photostabi -y of Pyrethroidal Compounds. Botyu Kagaku, 3 102.

7

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CHARTS - RAT METABOLISM 1 to 8

1

Casida,J.E., Kimmel, E.C., Elliott,M. & Janes, N.F. (1971) "Oxidative Metabolism of Pyrethrins in Mammals" Nature,Vol. 230 pp 326-327 2

Casida, J. E., & Ruzo, L.O. (1980) Pestic. Sci. Vol 11, pp 257-269 "Metabolic Chemistr of Pyrethroid Insecticides"

3

ELLIOTT, M., JANES, N.F., Kimmel, E.C. & Casida, J.E. (1972)"Metabolic Fate of Pyrethrin i, Pyrethrin 2, and Allethrin Administered Orally to Rats" Agric. & Food Chemistry. Vol. 20, No 2, pp 300313. 4

Hutson D.H. Revie : "The Metabolic Fate of Synthetic Pyrethroid Insecticides in Mammal in Progress in Drug Metabolism. Vol 3 Ed. L.F. Chasseaud & Bridges, J.W. John Wiley & Sons London 1979. pp 215-252. 5

Chambers, J. (1980)"An Introduction to The Metabolism of Pyrethroids" Residue Reviews, No 73 pp 101-124.

6

Soderlund D.M. & Casida J.E. (1977) "Effects of Pyrethroid Structure on Rates of Hydrolys and Oxidation by Mouse Liver Microsomal Enzym Pesticide Biochemistry & Physiology Vol 7, pp 391-401 7

Fairfield American Corp. Analytical Methods for Pyrethrins by HPLC and GLC.FAC-3 & 20.

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REVIEWER

APR 18 1988

006667

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: EPA File Symbol 52563-R: Pyrethrins. Toxicology Branch response to the inquiry from John W. Kennedy consultant to the U.S. Pyrethrum Culture concerning registration of dried pyrethrum flowers grown in the USA and shipped to refineries for processing to pesticide products.

TOX CHEM No.: 715
TOX PROJECT No.: 8-0400
Record No.: 187933

FROM: John Doherty 4/14/88
Toxicology Branch
Hazard Evaluation DIvision (TS-769)

TO: Phil Hutton
Product Manager #17
Registration Division (TS-767)

THROUGH: Edwin Budd
Section Head
Toxicology Branch
Hazard Evaluation Division (TS-769)

4/14/88 4/18/88

Mr. John W. Kennedy, consultant for the U.S. Pyrethrum Culture, has submitted a collection of published articles from the general literature regarding various aspects of pyrethrum toxicity, metabolism and chemistry. Mr. Kennedy is requesting that the information be used in support of the registration of their product dried chrysanthemum flowers containing pyrethrin grown in the USA. These flowers will be packaged and shipped to manufacturers where they will be processed into refined pyrethrin and formulated into pesticide products. Mr. Kennedy asserts that most of the data developed on pyrethrins is "public" and can be used to support the registration of pyrethrins grown in America as well as elsewhere.

Toxicology Branch Response

1. TB has surveyed the information provided by the U.S. Pyrethrum Culture and notes that most of the information has already been made available to the Agency. Most of these studies would have to be classified as either SUPPLEMENTARY or INVALID according to the current guidelines for toxicity testing because of incomplete data submissions or the study designs are not consistent with current standards.

2. The formal toxicity data base for pyrethrins is in the process of being updated and newer studies using current guidelines for toxicity testing are being provided by the Pyrethrin Joint Venture/Chemical Specialties Manufacturers Association (PJV/CSMA) in response to a DATA-CALL-IN notice previously issued by Registration DIvision of OPP. These studies are being conducted with a blend of pyrethrin plus stabilizers and solvent that was previously agreed upon between Toxicology Branch (TB) and PJV/CSMA group (refer to memo from J. Doherty July 15, 1986 for EPA Id. No.: 069001).

TB expects that these studies if found to be acceptable to the Agency will be used to support the registrations and tolerances for pyrethrins. The U.S. Pyrethrum Culture group may not be able to use these studies to support the registration of their product without prior compensation to the PJV/CSMA group. Such proprietary concerns are not the responsibility of TB.

3. TB noted that a paper on the metabolism of radiolabelled pyrethrins I and II and allethrin (refer to DER attached) was included. This paper described the synthesis of ^{3}H and ^{14}C labelled pyrethrin I and II and proposed pathways for their metabolism based on identification of urinary and fecal metabolites. This study has been assigned SUPPLEMENTARY classification but provides information that is considered useful to the overall problem of the metabolism of pyrethrins.

006667

Reviewed by: J.D. Doherty 4/14/88
Section II, Tox. Branch (TS-769C)
Secondary reviewer: E.R. Budd
Section II, Tox. Branch (TS-769C)

DATA EVALUATION REPORT

STUDY TYPE: General Metabolism:Rats and MIce TOX CHEM No.: 715

ACCESSION NO.: Not Provided MRID NO.: Not provided

TEST MATERIAL: Radiolabelled (^{3}H and ^{14}C) pyrethrins (I and II) and allethrin.

SYNONYMS: N/A

STUDY NUMBER(S): None provided (journal publication)

SPONSOR: None

TESTING FACILITY: University of California, Division of Entomology Berkeley, California

TITLE OF REPORT: "Metabolic Fate of Pyrethrin I and Pyrethrin II and Allethrin ADministered Orally to Rats.

AUTHOR(S): M. Elliott, N.J. Janes, E.C. Kimmel and J.E. Casida

REPORT ISSUED: In Journal of Agriculture and Food Chemistry 20(2) 300-313 (1972).

CONCLUSIONS:

The publication reports on the synthesis of radiolabelled pyrethrins I and II and allethrin and how these were metabolized by rats and mice. The methods used for the analysis and identification of the metabolites were extensively described and several metabolites identified. See review.

Classification: CORE-SUPPLEMENTARY. The data are presented in a publication form and no original data are included.

Special Review Criteria (40 CFR 154.7): N/A.

Quality Assurance Statement: None provided. Study is circa 1970 and is a published literature citation.

REVIEW

In this experiment both radiolabelled (with ^{3}H and ^{14}C) and unlabelled pyrethrin I and pyrethrin II were utilized. The unlabelled pyrethrins I and II were made by "reconstitution from the acid and alcohol moieties isolated from the natural esters" The radiolabelled Compounds were prepared by methods developed over a span of several years by Dr. J.E. Casida and his colleagues. ^{3}H was generally used to label the pyrethrins in the alcohol moiety and ^{14}C was used to label the cyclopropane carboxy groups.

The rats (male, Sprague-Dawley young adult) were dosed for either tracer studies with low dose (1-5 mg/kg) to determine the isotope content of the urine and other factors of metabolic and pharmacokinetics. In another set of experiments designed to collect large quantities of metabolites, the pyrethrins were given orally for a total of 1.10 g of pyrethrin I and 2.4 g of pyrethrin II. In still another set of experiments, male mice were dosed with 1-5 mg/kg of the $1^{4}C$ pyrethrins and the ^{14}C content of the urine and expired air were monitored. The test materials were dissolved in DMSO and administered via stomach tube.

The paper described the various methods and procedures used to isolate the urinary and fecal metabolites, enzymatic cleavage of conjugates, the radioactivity balance studies and chromatography systems and spectroscopy used in analysis of the metabolic pathways.

The proposed metabolic scheme or pathway for pyrethrins I and II is shown in Figures 2 (xeroxed from the study report). The initial step in this metabolic scheme appears to be oxidation of the vinyl side chain to a carboxylic group. This is followed by oxidation of side chain of the alcoholic side chain to form first an epoxide and subsequently diol which are in turn conjugated. The metabolic pathway for allethrin in rats was also studied and is shown in Figure 3 (xeroxed from the study report). The initial step in the metabolism of allethrin is apparently the same for pyrethrins I and II. It is noted that esteratic cleavage of these chemicals is apparently not a major route of metabolism. Table I (xeroxed from the study report) shows the distribution of the radioactivity among the metabolites in the urine and feces.

One problem that must be resolved regarding this study concerns the actual chemical synthetized (both radiolabelled and unlabelled). For example, are these chemicals the same stereo-specific isomers as the natural pyrethrins. If they are, the method(s) of proving the identity must be provided.

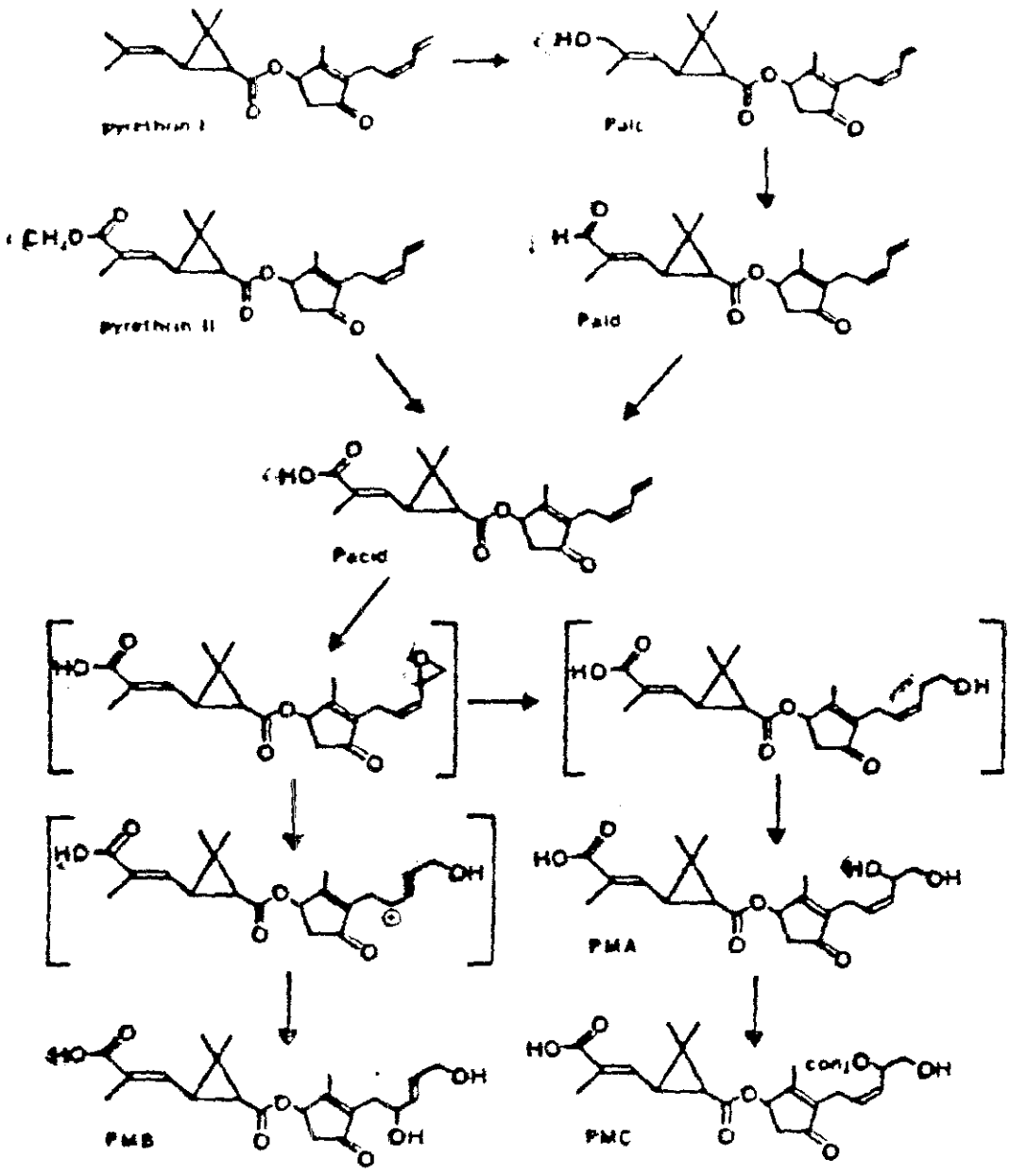


Figure 2. Tentative metabolic pathway for pyrethrins I and II in rats

the products were dissolved in deuterochloroform and filtered through a cottonwool plug into a nmr tube. After determining the nmr spectrum, the sample was subdivided for further analysis, particularly by ms, as described below.

Enzymatic Cleavage of Conjugates. The possibility that some of the metabolites of pyrethrin I occur in the urine as conjugates was tested by attempting to cleave them enzymatically with glusulase. An aliquot of the urine from rats given pyrethrin I [PyI-^{14}C(O)O-acid] was evaporated to dry-

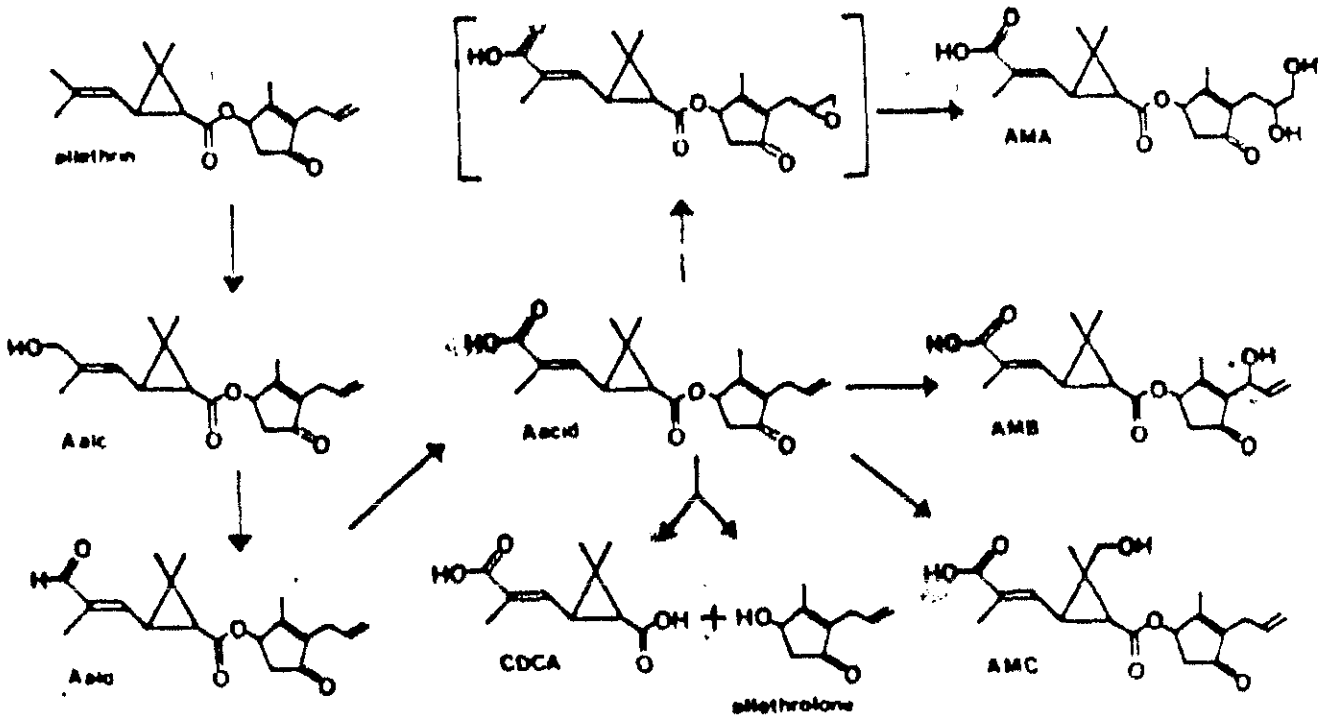
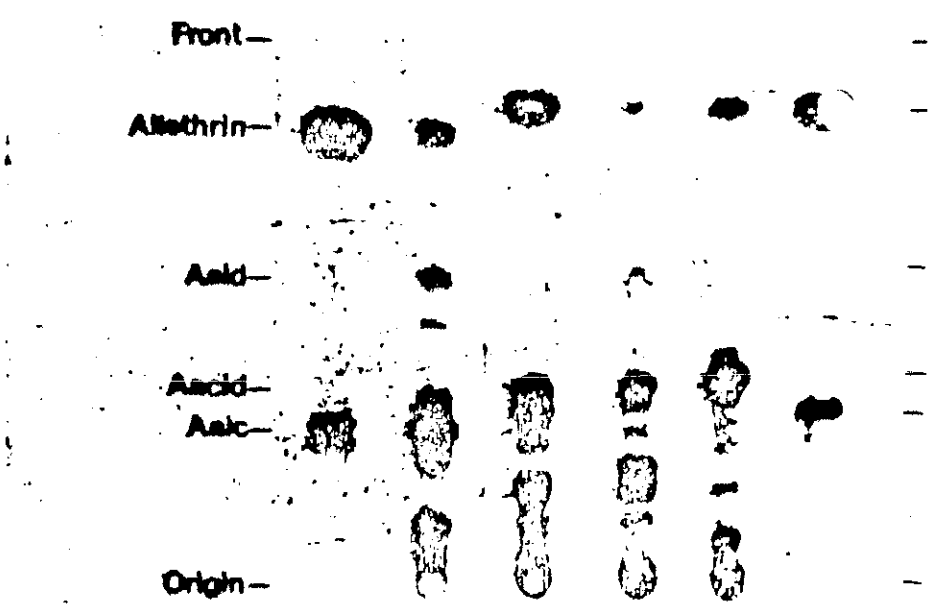


Figure 3. Tentative metabolic pathway for allethrin in rats

sional tlc, the chromatoplates were developed with benzene, air-dried, and then developed with the BFE1 solvent system. For two-dimensional tlc, the chromatoplates were developed with benzene and then with the EMBF solvent system in the first direction, followed by the EBMF solvent system in the second direction. All products obtained from various enzyme preparations were compared by one-dimensional tlc. In addition, two-dimensional cochromatography was used to compare the metabolites of pyrethrins I and II from the rat liver microsome–NADPH enzyme system with those in the urine of rats treated orally with pyrethrins I or II.

Radioactivity Balance Studies. The metabolism cages, the methods for collecting the urine, feces, and expired CO_2, and



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9% and AI-^{3}H-alc
the feces. Allethrin

Table I. ^{3}H-Compounds Present in the Urine and Feces of Male Rats 100 Hr after Receiving 3 mg per kg of Pyrethrin I-^{3}H-alc or Pyrethrin II-^{3}H-alc, Orally

^{3}H-Compounds	Administered ^{3}H Recovered, %[a]		
	Urine	Feces	Total
	Pyrethrin I administered		
Pyrethrin I	0.0	18.0	18.0
PMA[b]	9.5	4.8	14.3
PMB	2.9	1.5	4.4
PMC	1.8	2.1	3.9
Unknowns			
Less polar (PMD)	0.0	1.4	1.4
More polar (PME and PMF)	16.0	13.2	29.2
Total	30.2[c]	41.0[c]	71.2
	Pyrethrin II administered		
Pyrethrin II	0.0	4.0	4.0
PMA[b]	15.8	5.3	21.1
PMB	2.1	1.2	3.3
PMC	2.8	3.4	6.2
Unknowns			
Less polar (PMD)	0.0	3.0	3.0
More polar (PME and PMF)	12.3	13.8	26.1
Total	33.0[c]	30.7[c]	63.7

[a] Analyses of the proportion of individual metabolites in urine samples at 6-hr intervals during the first 24 hr after treatment and in feces samples at 0–20, 20–28, and 28–48 hr after treatment showed no significant deviations from the overall average values presented. [b] Includes a small amount of PMA' not adequately resolved for separate analysis. [c] The percentages of the administered ^{3}H excreted in the 0–20, 20–48, and 48–100 hr intervals were as follows: pyrethrin I, urine 23.2, 5.5 and 1.5; feces 14.8, 23.3, and 2.9; pyrethrin II, urine 24.6, 6.7 and 1.7; feces 16.6, 11.4, and 2.7.

Isolation of Urinary Metabolites of Pyrethrin I, Pyrethrin II, and Allethrin. The metabolites were separated on three columns in succession. Much interfering material was first removed by a preliminary separation on a column of silicic acid–Celite. Next the metabolites were methylated with diazomethane to improve their chromatographic behavior and alter their polarity relative to that of impurities still present. This step involved loss of material, but permitted greater purity to be eventually attained. Table II gives the solvents and packings for the column purification of metabolites and the tlc systems with R_f values used to assess their purity.